Chemotherapy Induced Neutropenic Fever and Its Response to Empirical Antimicrobial Therapy

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ABSTRACT

Objective: To find out the frequency of chemotherapy-induced febrile neutropenia (FN) in children diagnosed with Acute Lymphoblastic Leukemia (ALL) and its response to empirical antibiotic therapy.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Peadiatric Oncology, Combined Military Hospital, Rawalpindi Pakistan, from Nov 2017 to Oct 2018.

Methodology: Newly diagnosed pediatric patients suffering from acute lymphoblastic leukemia between 1 to 15 years of age were included. All patients were treated with chemotherapy according to the United Kingdom National Randomized Trial for Children and Young adults with Acute Lymphoblastic Leukemia (UKALL) 2011 protocol. Patients with febrile neutropenic (FN) episodes were treated with empirical antimicrobial therapy as per hospital guidelines. Patients 'response to antimicrobial therapy, blood culture results and related complications were noted.

Results: Out of a total 77 patients, 45 (58.4%) had 69 episodes of febrile neutropenia (FN), 62 (78.5%) episodes of febrile neutropenia (FN) were started empirical treatment with first-line antibiotics (piperacillin-tazobactam and amikacin) whereas 15 (21.7%) episodes of febrile neutropenia (FN) not responding to the 1st line were shifted to second-line antibiotics (meropenem and amikacin). Mean duration of fever was 4.1 ± 2.8 days on 1st line antibiotic regimen, 2.6 ± 1 days on 2nd line antibiotics and 6.3 ± 3.3 days on combination with antifungal drug. Ten patients received antifungal therapy empirically. Efficacy of the 1st line and the 2nd line was 72.5% and 77% respectively. Staphylococcus aureus was the most frequent organism isolated from blood culture results. During the induction phase, 10 (12.9%) patients expired.

Conclusion: Majority of patients responded to empirical 1st and 2nd line antibiotics. Treatment-related mortality due to infection is quite high in our setup.

Keywords: Acute lymphoblastic leukemia, Chemotherapy-induced febrile neutropenia, Empirical therapy, Febrile neutropenia (FN), Neutropenic fever.

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INTRODUCTION

Chemotherapy-induced febrile neutropenia(FN) is a known complication of chemotherapy leading to morbidity andmortality. Paediatric oncology patients with neutropenia during chemotherapy are susceptible to infectious agents, and therefore demandtreatment with broad-spectrum parenteral antibiotics.[1,2] This condition is an economic burden on society as the management of patients is costly during this complication where supportive care is necessary.[3] Although chemotherapy target complete granulocytic lineage, but neutrophils make a major defense against bacterial infections and we need to be vigilant when they are low as opportunistic infectious agents may encounter immune system.[4] These neutropenic patients are prone to develop overwhelming infections which can be fatal within no time. Patients with an absolute neutrophil count (ANC) of ≤0.2 × 10^9 /L are required to provide hospitalization and antibiotic administration.[5] Chemotherapy can compromise the defense of cutaneous/ mucosal surfaces as well as the nutritional status of the patient, which further predisposes the patient to infection as the immunocompromised state is developed.[6]

There is a paucity of data regarding the duration of antibiotic therapy in patients with neutropenic fever. However, a more stringent antibiotic stewardship which may reduce treatment duration is not yet established.[7] Keeping in view the low yield of blood culture in chemotherapy-induced FN patients the trend of FN and its response to empirical therapy in any oncology unit needs to be studied to aid in empirical antibiotic stewardship.[8,9]

The objective of this study was to have an overview of trend of neutropenic fever (referred as febrile neutropenia), complications related to this

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condition during chemotherapy of acute lymphoblastic leukemia and its response to empirical antibiotics being used in the paediatric oncology unit.

METHODOLOGY

It was a cross-sectional study conducted at the Paediatric Oncology unit of Combined Military Hospital, Rawalpindi, Pakistan from November 2017 to October 2018 according to recommendations from International Ethical Guidelines and after prior approval from Ethical committee of Combined Military Hospital (CMH). The paediatric patients with an age group from 1-15 years who were suffering from Acute Lymphoblastic Leukemia (ALL) were included in the study during remission induction chemotherapy.

Informed consent was taken from parents/ guardian of all patients registered in our study. All patients were treated with chemotherapy according to the UKALL 2011 protocol.

Patients suffering from severe Febrile Neutropenia (FN) and having Absolute Neutrophil Count (ANC) of less than 500/mm3for a day or more and the patient labeled as febrile with a single oral temperature of 38.3°C or three consecutive temperature readings of 38°C (100.4° F), >4 hours apart within 24 hours period were included in the study.

Patients havinga fever with cause other than chemotherapy-induced febrile neutropenia, Fever episodes observed within 24 hours after the commencement of chemotherapy and developing fever within 4 to 6 hours after transfusion of blood or bloodproducts were all excluded from the study.

All patients underwent thorough clinical assessment and their absolute neutrophilcount (ANC) and administered antimicrobials were noted. All patients were administered with empirical antimicrobial therapy according to Infectious Disease Society of America (IDSA),[4] and American Society of Clinical Oncology (ASCO) guidelines,[10] when the 1st episode of febrile neutropenia occurred in patients. We assessed the efficacy of two antibiotic regimens and the most frequently used antibiotic was piperacillin-tazobactamin combination with an aminoglycoside (amikacin) and labeled as 1st line antibiotic regimen. Patients with profound neutropenia (ANC ≤0.1 cells/mm^3) and those not responding to the first-line antibiotic regimen (after 48 hrs) were started on meropenem + amikacin and labeled as 2nd line antibiotic regimen.Teicoplanin was added to the treatment regimen in patients with no response to 2nd line antibiotics having evidence of severe sepsis, skin or soft tissue infection or documented pneumonia on chest x ray as shown in Table-I. Blood specimens of few patients were sent to the laboratory for culture and sensitivity. Treatment was tailored for positive culture and sensitivity results. Patients with *Methicillin-Resistant Staphylococcus aureus* (MRSA) positiveon culture also received teicoplanin. Amphotericin B was added to the antibiotic regimen as a broad-spectrum antifungal agent, for patients with persistent fever >96 hours as per IDSA guidelines.[4,10] The response rate/efficacy of these empirical antimicrobials was calculated. All patients were screened for renal dysfunction and other comorbidities. If patients showed the absence of symptoms or have no fever for three or more successive days along with rising ANC, this was considered as successful antibiotic therapy. Antibiotictherapy was stopped after the patient remained afebrile for 48 hours provided the neutrophilcount was ≥500 /mm^3 for two successive days without any apparent focus of infection.Antibiotics were continued for five successive days after patients became afebrile if the neutrophil count was <500/mm^3.

Statistical Analysis

T-test, one way ANOVA and chi-squared (Goodness of fit) were used for comparison between continuous and categorical variables. All statistical analysis were performed using the Microsoft Excel and *p*-value of less than 0.05 was considered statistically significant. We fail to reject the null Hypothesis at $\alpha = 0.05$, and conclude that the proportions of various genders are equal (*p*=0. 5 each)

RESULTS

During the study period of one year, a total of 77 (n=77) paediatric patients diagnosed as Acute Lymphoblastic Leukemia (ALL) were evaluated for febrile neutropenia (FN), related complications and its response to empirical antibiotics therapy. Male 46 (60%) to female 31(40%) ratio was found to be 3:2 with a mean age of 5.8 ± 3.8 years as shown in Table -I. Out of these (n=77) patients, 45 suffered from FN making a percentage of 58.4% patients who experienced a total of 69 episodes of FN with a maximum of three episodes per patient. Sixty-two (78.4%) episodes of FN were started treatment with first-line antibiotics as shown in Table-I.

From these 62 FN episodes, 15 (21.7%) were shifted to second-line antibiotics while 10 (14.4%) FN episodes lasting >96 hours were added with antifungal therapy. The response rate of 1st and 2nd line

antimicrobials, and antifungal drugs are shown in Table-II.

Complications during inpatient management were also seen in patients which are mentioned in Table-I. Out of n number (77) of patients, 23 (29.8%) had no complications except febrile neutropenia (FN), 4 (5%) patients had sepsis and abdominal pain each and rest other complications are shown in Table-I.

Table-I: Patient age, gender, and types of acute lymphoblastic leukemia.

Variable	n (%)	Mean ± SD	*p*-value
Gender			
Female Male	31 (40%) 46 (60%)		0.08738 Chi square (Goodness of fit) H0: $\chi^2 = 0$ Ha: $\chi^2 > 0$ χ^2= 2.9221 df = 1 *p*-value <0.08738 Interpretations: We fail to reject the null Hypothesis at $\alpha = 0.05$, and conclude that the proportions of various genders are equal (*p*=0. 5 each)
Age in Years			
1-7 group 7-15 group	56 (72.7%) 21 (27.3%)	5.8 (± 3.5)	
Acute Lymphoblastic Leukemia Types			
Pre-B Acute Lymphoblastic Leukemia T-Acute Lymphoblastic Leukemia	75 (97.4%) 02 (2.6%)		
Treatment related mortality (TRM)	10 (12.9%)		
Febrile Episodes Patients First Episode Second Episode Third Episode	- - 27 (60%) 12 (26.6%) 06 (13.4%)		0.00073
Tested for Blood Culture			
Gram-Positive Isolates Staphylococcus Aureus Cons. Aureus Gram-Negative Isolate	05 (12.5%) 03 (7.5%) 02 (5%) Nil		
Complications			
Only febrile neutropenia Sepsi Respiratory failure Abdominal pain Mucormycosis Fits Paralytic ileus Gastric bleed Cerebellar abscess Miscellaneous *	23 (35.5%) 04 (06%) 02 (03%) 04 (06%) 02 (03%) 03 (4.5%) 01 (1.5%) 02 (03%) 01 (1.5%) 24 (36%)		

Lung Abscess, Osteomyelitis, Oral Herpes, Mucositis, Lymphadenitis, Cellulitis

Table-II: Empirical antimicrobial response to Febrile Neutropenic episodes.

1st Line Antibiotics	Total Febrile Neutropenic Episodes Received	Overall Efficacy	Mean Duration of Febrile Days (Means ± SD)
Piperacillin + tazobactam + Amikacin	62	45/62 (72.5%)	4.1 ± 2.8
2nd Line Antibiotics			
Meropenem + Amikacin	7+15*= 22	17/22 (77.2%)	2.6 ± 1
Other Combination			
Meropenem + Teicoplanin	5	3/5 (60%)	
Antifungals			
Amphotericin B	10	6/10 (60%)	6.3 ± 3.3

15 febrile neutropenic episodes shifted to the 2nd line after no response to 1st line antibiotic

Maximum three episodes of FN were recorded per patient during remission induction. Overall, we observed 69 episodes of febrile neutropenia in 45/77 patients. Out of these 45 patients with febrile episodes 12 (26.6%) experienced 2 episodes of FN and 6 (13.4%) experienced 3 episodes of FN per patient, while remaining 27 (60%) patients experienced only 1 episode of FN, details of episodes are shown in Table-I. Some patients with FN meeting exclusion criteria were not added. Eleven patients (14%) did not show any FN episode. Mean duration of fever was 4.1 ± 2.8 days on 1st line antibiotic regimen (piperacillin-tazobactam + amikacin), 2.6 ± 1 days on 2nd line antibiotic regimen (meropenem + amikacin) and 6.3 ± 3.3 days on combination with the antifungal drug as shown in Table-II.

Ten (12%) patients expired during remission induction. However, patients having long duration (>4 days) of FN and requiring antifungal were having high mortality of up to 40%. *Staphylococcus aureus* was the most common pathogen isolated from the blood culture of patients whose culture was possible as shown in Table-I.

DISCUSSION

Children suffering from Acute Lymphoblastic Leukemia (ALL) undergo chemotherapy administration and are vulnerable to develop infections especially during the remission induction phase. Infections remain a leading cause of death in patients undergoing chemotherapy in spite of the marked improvement in supportive care.[11] Management of such patients demands the administration of empirical therapy without any delay and serial evaluation to assess and modify the therapeutic response.

Initiation of treatment and later modifications are mainly clinical decisions of treating physician and occasionally linked with results of blood or fluid culture. The focus of our study was to assess the response of febrile neutropenic (FN) patients to empirical antimicrobial therapy.

In our study first line antibiotic regimen included piperacillin-tazobactam and amikacin. Second line regimen included meropenem and amikacin. These regimens were well tolerated. Antimicrobial drugs used to treat infection were according to the guidelines of ASCO which recommends piperacillin-tazobactam and amikacin as an empirical use following chemotherapy.[10] A Swedish cohort study of children documented the use of piperacillin-tazobactamas a first-line empirical antibiotic therapy in many centers. The preferred antibiotics for children with neutropenic fever were penicillin withinhibitors followed by carbapenems, aminoglycosides, and glycopeptides.[7]

The response rate (72.5% and 77%) to empirical antimicrobial therapy in our study came to be higher when compared to the culture-based study conducted in the same institute (CMH Rawalpindi) in which combination of amikacin and ceftazidime showed 61.3% response in various childhood malignancies.[12]

In one study conducted by Viscoti *et al,* two antibiotic regimens, ceftazidime plus amikacin and ceftazidime plus vancomycin were assessed in a randomized clinical trial as empiric therapy in febrile neutropenic children with cancer. It showed a response rate of 66% vs. 77%.[13]

In another study conducted by Riikonen, two antibiotic regimens were assessed, imipenem as monotherapy and ceftazidime plus vancomycin as combination therapy, for initial empiric therapy in febrile neutropenic children with cancer. It showed 82% efficacy in imipenem and 59% in ceftazidime plus vancomycin group.[14]

In a study conducted by Abraham *et al,* at Bharati hospital, Pune in 2019; 32% of paediatric patients suffered from febrile neutropenia and Staphylococcus species (49%) were the most common one which was positive in blood culture,[15]however in our study most of the cultures were negative and only two culture were positive for *S. aureus*.

Patients with persistent fever (>4 days) and neutropenia were added empirical antifungal drug (Amphotericin B) to treat occult fungal infection and prevent fungemia as it is prevalent in an immunocompromised state. Besides mucositis and mucormycosis no fungal infection was documented in our study, which is comparable to other studies.[15] Invasive fungal infections contribute significant morbidity and mortality in neutropenic patients on chemotherapy. Thus, a delay in treatment while establishing a diagnosis leads to increased morbidity and mortality.[16]

In this study, treatment-related mortality (TRM) was 12.9% (10/77) and sepsis was the major cause of mortality (90%). Similar results were documented by Asim *et al,* from 2001 to 2005 at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCHRC), Lahore Pakistan. They documen-ted 12.8% (39/304) mortality in ALL patients during the induction phase of therapy and showed 85% infection-related mortality out of total deaths.[11] There was 40%

(4/10) mortality in our patients requiring antifungal therapy as shown in Table-II with an efficacy of 60%.

Regardless of identification ofthe causative organism, it is a common clinical approach to continue empirical antimicrobials in FN patients untilthe fever has settled along with a rise in ANC. Previousstudies have documented a median of two episodes of neutropenic fever per child undergoing chemotherapy.[7] While in our study 26.6% (12/45) of patients were observed with two episodes and 13.4% (6/45) with three episodes of Febrile Neutropenia (FN) as shown in Table-I.

Treatment of children experiencing febrile neutropenia demands admission and broad-spectrum antibiotics. Overall, the rationale for the use of antibiotics in paediatric patients with malignancy in relation to bacteriological findings and treatment span needs to be established.[7] The National Institute for Clinical Excellence (NICE) guidance improving outcomes with children and young people with cancer statedthat ''national research is required for: the development of robust methods of risk stratification in the management of FNP'' and ''the exploration of the safe introduction of shorter periods of inpatient admission and/or community-based therapy for low-risk episodes.[17]

The response rate to 1st and 2nd line antibiotics in our setup could be compared with data from other studies from Pakistan and developed countries but treatment-related mortality (TRM) was high due to infection.[18] More multicenter studies are needed to establish a standard approach to decide the need of blood culture and to define optimal initial empirical antimicrobial therapy, its duration and risk stratification in a way that sustains safety, minimizes financial burden and maximizes the quality of care by reducing overall treatment-related mortality in FN children with common malignancy.

CONCLUSION

Majority of patients responded to empirical 1st and 2nd line antibiotics. The current practice for empirical broad-spectrum parenteral antibiotic therapy is safe and productive. Children presenting with fever and neutropenia without apparent signs of sepsis require immediate treatment with broad-spectrum antibiotics. When patients are afebrile, clinically well along withthe improved neutrophil count, antibiotics can be safely discontinued.

LIMITATION OF STUDY

Keeping in view poor yield of blood culture results, the chance of contamination, iatrogenic blood losses, consumption of extra time and skills and thus a financial burden to the patient, culture, and sensitivity methods were not focused in all patients in our current study.

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Conflict of Interest: None.

Author's Contribution

HMM: Substantial contribution, design and analysis, SM: Design and analysis, MSI: Design and data interpretation, TG: Conception and design, AAA: Theme and analysis, NF: Theme and data interpretation.

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